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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,625	07/02/2003	Warren D. W. Heston	41426-GC/JPW/CY	7841

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EXAMINER

BORGEEST, CHRISTINA M

ART UNIT	PAPER NUMBER
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1649

DATE MAILED: 10/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/614,625	Applicant(s) HESTON ET AL.	
	Examiner Christina Borgeest	Art Unit 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on _____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 24-35 is/are pending in the application.
- 4a) Of the above claim(s) 26-35 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) _____ is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 02 July 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>12/04; 3/04; 6/04; 4/05</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 24-25 in the reply filed on 27 July 2006 is acknowledged. Note there was also a species election requirement, and Applicant has elected to prosecute methotrexate triglutamate (MTXglu₃). The traversal is on the ground(s) that Groups I-III are not independent because Group I provides therapeutic methods involving the inhibition of prostate specific membrane antigen (PSMA) and Groups II and III provide related compositions, thus the inventions of Groups I-III are not independent and that even distinct inventions must be examined if the search and examination can be made without serious burden. Applicants further argue that prior art with regard to Group II would identify art for Group III.

These arguments have been fully considered but are not found persuasive for the following reasons. First, the inventions I and II-III a process of use and products, respectively and can be properly restricted if it can be shown that **either** (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). Since the process of inhibiting the release of glutamate by N-acetylaspartylglutamic acid (NAAG) can be achieved by a product other than those described in Groups II and III, for instance, quisqualate (see Stauch et al. (Neurosci Lett. 1989; 100: 295-300), the Examiner has met the burden of showing that Groups I and II-III can be properly restricted. As to the argument that Groups II and III

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are related compositions and a search could be carried out without serious burden.

Groups II and III are not identical products because Group III requires "at least one therapeutic agent", thus there is an extension of search necessary to examine Group III.

Furthermore, the products in Groups II and III are not obvious variants, thus art that would obviate or anticipate Group II would not obviate or anticipate Group III. The requirement is still deemed proper and is therefore made FINAL.

Claims 26-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 27 July 2006. Claims 24-25 are pending and under consideration inasmuch as they are drawn to a method comprising administering an inhibitor of the neurocarboxypeptidase activity of PSMA so as to inhibit release of glutamate by NAAG hydrolysis, wherein the inhibitor is MTXglu₃.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: it is noted that only three inventors signed the declaration as compared to the five listed on the original unsigned declaration as well as on the first page of the specification, transmittal letter, and other correspondences. Applicants are reminded that a petition is needed to delete named inventors. Correction is required.

Information Disclosure Statement

The information disclosure statement filed 30 March 2004 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because page 1 contains what appears to be unpublished PCT documents; p. 2 contains a duplicate (EP 0173951); pps. 7-8 contain unpublished U.S. applications. It has been placed in the application file, but the references in question have not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Priority

Applicant designated the instant application as a continuation of 08/705,477, filed 29 August 1996, now U.S. Patent No. 6,569,432. While this application repeats a substantial portion of the '432 application, the amendment filed 7 July 2003 adds substantial additional disclosure not presented in the prior application. Since this application names an inventor or inventors named in the prior application, it constitutes a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. 120 and 37 CFR 1.78, and the first paragraph of the specification must be corrected accordingly.

Specification

The abstract of the disclosure is objected to because it is three paragraphs.
Correction is required. See MPEP § 608.01(b).

Claim Objections

Claim 25 is objected to because of the following informalities: The claim recites non-elected species. In addition, in the interest of clarity it is suggested that the Applicant spell out methotrexate triglutamate followed by the abbreviation in parenthesis (MTXglu₃). Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims do not specify to what or to whom the agent is administered, this method step is incomplete.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for therapy comprising administering MTXglu₃ to cells comprising prostate specific membrane antigen (PSMA), does not reasonably provide enablement for administering inhibitors of NAAG hydrolysis to cells as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 Fed. Cir. 1988) These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The first issue is the breadth of the claims. Applicants have broadly claimed administration of any inhibitor of NAAG hydrolysis, and the broad recitation would prevent the public from administering any compounds that are yet to be discovered that inhibit NAAG hydrolysis. Another issue that comes up under breadth is that Applicants do not specify in the claims that in order for the method to work the NAAG inhibitor (i.e.,

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MTXglu₃) must be administered to the cells expressing PSMA. The claims merely recite “[a] method comprising administering an inhibitor...”, thus encompasses administration to any cells, or persons lacking PSMA, for instance, females. The specification states at pps. 105-106:

[MTXglu₃] was used to examine the action of this compound on the in vitro growth of PC-3 cells transfected with a plasmid with a selectable marker versus a plasmid with a selectable marker that expresses PSM antigen as well the PC-3 cells that were transfected with PSM were inhibited 85% in growth by day four by 10 uM [MTXglu₃], while the PC-3 plasmid only transfectants did not exhibit any significant inhibition of growth.

Thus it is clear in the specification that the claimed method is only works on PSMA positive cells or cells that were transfected with PSMA, because according to the specification, cells that did not express PSMA did not experience any growth inhibition with the administration of MTXglu₃. The inventors provide no evidence or direction as to how the invention could be practiced on cells not expressing the PSMA, nor are there any working examples directed to the same, on the contrary, the specification clearly states that the method worked only in PSMA positive cells.

The nature of the invention is complex; although the claims are not limited to therapy they encompass therapy and the specification contemplates prostate cancer therapy. For instance, in the added matter to p. 105 of the specification (in the amendment filed 2 July 2003), the inventors discuss prostate cancer and how “[p]rostate cancer has always been absolutely refractory to methotrexate therapy...” In the same paragraph, the Applicants contemplate the reasons for this, namely that methotrexate is a prodrug that requires polyglutamation to its metabolites to be effective and that folate hydrolase deglutamates methotrexate, causing it to diffuse back out of

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the cell. However, the specification does not provide support for the treatment of any type of cancer with any inhibitor of NAAG hydrolysis, thus the scope of the claims is not commensurate with what is taught in the specification.

Due to the large quantity of experimentation necessary to determine how the invention could be practiced in cells lacking the PSMA, the lack of direction/guidance presented in the specification regarding and the absence of working examples directed to the same, the complex nature of the invention (cancer therapy), the state of the prior art, and the breadth of the claims which fail to recite limitations on the inhibitors or fail to recite the recipients of the inhibitors of NAAG hydrolysis, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Curt et al. J Clin Invest. 1985; 76: 1323-9, (see abstract), which teaches that certain diseases are resistant to methotrexate therapy due to a lack of polyglutamation of the prodrug. Serval et al. (J Neurochem. 1990; 55: 39-46) teach that NAAG inactivation occurs through enzymatic hydrolysis into N-acetyl-L-aspartate and glutamate by an N-acetylated-alpha-linked acidic dipeptidase (NAALADase), and that quisqualate is a non-competitive inhibitor of NAALADase, thus inhibits NAAG hydrolysis (see abstract).

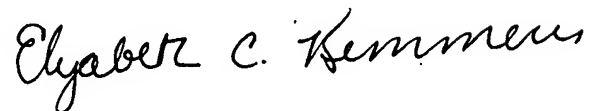
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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is 571-272-4482. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest, Ph.D.



ELIZABETH KEMMERER
PRIMARY EXAMINER